



# national tay-sachs & allied diseases association RESEARCH REVIEW | May 26, 2017

## 2017 NTSAD RESEARCH INITIATIVE GRANT AWARDS

The 2017 Research Initiative Request for Proposals garnered 16 pre-applications. The grant topics included stem cell and gene therapy, biomarkers, novel drug delivery methods, and other topics included in our [Guidelines](#).

Through an intensive review process, six were invited to submit full applications. After evaluations by [Scientific Advisory Committee](#) (SAC) members, a grant recommendation from a subset of the SAC group was made to NTSAD's Executive Committee for approval. As a result, three grants have been awarded to the following researchers.

Funds are raised year round from many generous donors, including through family funds and the proceeds from NTSAD's Annual Day of Hope. Thanks to the many families and their friends who rally and raise funds and awareness for Day of Hope! Stay tuned for details on this year's Day of Hope in future emails.

# 56

Number of grants since the Research Initiative was created in 2002. See the list [here](#).

# 11

Number of active projects funded by NTSAD Research Initiative grant awards. See the list [here](#).

# \$3.8 million

Amount of funding that has led to over \$20 million dollars in funding from the NIH and similar institutions.

**Alessandra Biffi, MD**  
Director, Gene Therapy Program at  
Dana-Farber/Boston Children's Hospital  
Cancer and Blood Disorders Center  
Boston, MA

**Project:** Proof of concept study of HSC gene therapy for Tay-Sachs disease

### Goals of the Proposal

- To assess the feasibility and efficacy of an innovative gene therapy based on hematopoietic stem cells (HSCs) and lentiviral vectors (LVs) in the mouse model of Sandhoff disease (SD)
- To conduct a proof-of-concept study that could be translated into a

**Heather Gray-Edwards, PhD**  
Scott-Ritchey Research Center  
Auburn University  
Auburn, AL

**Project:** Minimally invasive delivery of AAV gene therapy in the Tay-Sachs Sheep

### Goals of the Proposal

- To evaluate efficacy of adeno associated viral (AAV) gene therapy after cerebrospinal fluid (CSF) delivery in the sheep model of Tay-Sachs disease (TSD)
- To confirm previously proposed biomarkers of TSD, including MRI image, lipidomic signatures,

larger scale study and future clinical development

### Impact of the Research

The project will test a novel gene therapy approach for TSD and SD with the potential for clinical translation. This gene therapy works by establishing a stable population of brain cells, which will serve as a sustained and balanced supply of the deficient enzymes in the patients.

Dr. Biffi and her research team accumulated extensive experience in preclinical development and clinical translation of gene therapies for lysosomal storage disorders (LSDs) and TSD. The proposed study has a high likelihood of achieving transformative outcomes in TSD/SD due to the investigators' expertise and the well-developed research plan.

Watch [this CBS Sunday piece](#) on Dr. Biffi's work on a gene therapy treatment for *Metachromatic Leukodystrophy (MLD)* [here](#).

cognitive testing, and neurologic evaluation

- To study the biodistribution and clearance of CSF delivered AAV gene therapy in the Tay-Sachs sheep

### Impact of Research

Gene therapy, is one of the most promising treatment options in development.

The study will evaluate the efficacy and biodistribution of the state-of-the-art gene therapy in TSD sheep. Tay-Sachs sheep is one of the most relevant animal models of the disease, due to its large brain size and suitability for various biomarker studies.

The findings in this proposal will aid in expanding our knowledge on the treatment's administration and biodistribution. The efficacy profile from the work with be necessary and helpful for future regulatory application before FDA. Most importantly, this study will generate useful data and insight about TSD biomarkers and contribute to future clinical studies in human patients.

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**Tim Wood, PhD, Greenwood Genetic Center. Greenwood, South Carolina & Stephane Demotz, PhD, Dorphan, Lausanne, Switzerland**

**Project:** Development of a quantitative method for the determination of a pentasaccharide in GM1-gangliosidosis patient cells to assess the potential therapeutic efficacy of a beta-galactosidase pharmacological chaperone drug candidate

### Goals of the Proposal

- To develop a quantitative, sensitive, and robust mass spectrometry based analytical method for the determination of a potential biomarker for GM1-gangliosidosis
- To explore treatment conditions of a drug candidate for GM1 in GM1-gangliosidosis patient cells using

## TAY-SACHS GENE THERAPY CONSORTIUM UPDATE

The ongoing IND-enabling studies funded by the National Tay-Sachs & Allied Diseases Association and Cure Tay-Sachs Foundation in GM2 mice and normal non-human primates (NHP) have shown no evidence of toxicity.

No abnormal symptoms were noted in any animals (of either species) treated with the maximum dose. Importantly the in-life portion of the study in GM2 mice was completed in April 2017 and results have met the pre-determined criteria for continuation to human clinical trials. Biochemical studies are ongoing to assess enzyme activity and GM2 storage clearance in the brain and spinal cord. Also, tissues have been collected, processed and placed in long term storage until funding can be secured for third party detailed histological and biodistribution analyses.

the analytical method developed in the first part of the project

### Impact of the Research

GM1-gangliosidosis and mucopolysaccharidosis IVB (MPS IVB) are two diseases caused by beta-galactosidase deficiency. A biomarker that indicates the severity and progression of the disease and a convenient analytic method to determine the biomarker will significantly enhance the clinical trial design in the therapeutic development.

A preliminary study found a potential biomarker for both GM1 and MPS IVB. The level of the biomarker, a sugar molecule, was elevated by 10 to 100 fold in the urine samples of GM1 and MPS IVB patients than samples of normal donors. This compound has the potential to be utilized as a biomarker for future clinical trials.

The findings from the proposed work will develop a quantitative method to analyze the sugar molecule, validate its role as biomarker for the diseases. In addition, researchers will explore the optimal treatment conditions of an investigational pharmacological chaperone drug candidate for GM1-gangliosidosis.

The short-term study in NHPs (3 mos) was completed in December 2016 with no clinical symptoms or gross evidence of toxicity at necropsy. The necessary tissues were collected and sent to a contract research organization (CRO) for processing and storage until funding is available to perform the necessary detailed histological examination of the brain and other tissues. A subset of NHP remain in good health more than 200 days after surgery and will be followed until one year (September, 2017), as requested by the FDA.

### Next steps

To get to the Investigational New Drug (IND) filing to start clinical trials, they have now checked off the animal studies, but still need to do the pathology studies of the animal tissues (as mentioned in the summary), manufacture clinical grade vectors, and hire a regulatory consultant.

**Support Research Here.**



Team NTSAD (left to right): Miguel Sena-Esteves, PhD, Heather Gray-Edwards, PhD, David Bradbury, Don Levick, MD, Staci Kallish, DO, Meredith Margolis, PhD, Allison Bradbury, PhD and NTSAD Research Initiative Chair, Jim Margolis, PhD, and Mary Levick, MD

## A BIG Thank You!

We thank the riders (pictured, left) and everyone who made a gift in support of Team NTSAD on the Fourth Annual Million Dollar Bike Ride.

The funds raised will go to funding a \$40,000 research project in the field of our rare diseases, but only if we raise \$20,000 so that it can be matched.

Help us get there. We have \$5,500 more to go until we hit that goal!

You still have time to make a gift and have it be matched to make a difference! The giving window is open until June 30th.

Make your gift [here](#) for **Team NTSAD**.

Thank you!

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***Forever Celebrating Cora***

*August 15th 2014 ~ May 23rd 2017*



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**Susan Kahn, Executive Director**  
**Brian Manning, President, NTSAD Board**  
**Fran Platt, PhD, Chair, Scientific Advisory Committee**  
**Veronica Huang, Science Communications Intern**

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